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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/482,585	01/13/2000	David G. Hangauer JR.	19226/931 (R-5495)	7206

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EXAMINER	
PONNALURI, PADMASHRI	
ART UNIT	**PAPER NUMBER**
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/482,585	Applicant(s) HANGAUER ET AL.	
	Examiner Padmashri Ponnaluri	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,13-20 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,13-20 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

NOTE the change of Examiner in this application.

The amendment and response filed on 7/31/03 has been considered and entered into the application.

Claims 2, 9-12, 21 and 23-69 have been canceled, claims 1, 3-8, 13-20, 22 are currently are pending and are being examined in this application.

In view of the amendment to the specification the objection to the specification set forth in the previous office action has been withdrawn.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

1. The disclosure is objected to because of the following informalities: the specification refers to the claim 1 method in page 37, lines 13-14.

Appropriate correction is required.

New Rejections necessitated by the Amendment

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 3-8, 13-20, 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The instant claims briefly recite a method for identifying inhibitors of protein kinases comprising: identifying at least one first module having one or more functional groups each capable of covalently or non-covalently binding to catalytic residues of the protein kinase; covalently attaching the atleast one first module to at least one second module comprises an indole to form one or more combinations of the first and second modules by substituting the at least one second module for the peptide scaffold; screening the one or more combinations of the first and second module for protein kinase inhibition; and selecting combinations o the first and second modules which inhibit protein kinase activity.

The specification disclosure is drawn to a method of identifying inhibitors of protein kinase comprising; a first module having one or more functional groups for binding to catalytic residues of protein kinase are combined with second module which provides for a non-peptide scaffold. The specification discloses non-peptide protein tyrosine kinase inhibitors having

specific formula (i.e., see page 5 of the specification). The specification discloses a descriptive method (in-silico method or hypothetical method) based on computer modeling of the kinases in identifying protein kinase inhibitors . The specification has not disclosed methods for identifying the functional groups on the first module (scaffold) which would bind to catalytic residues of the protein kinase and use the selected first module having a protein scaffold in attaching to a second module. The specification disclosure does not teach the claimed method steps in identifying a protein kinase inhibitor. The specification does not disclose identifying (covalently attaching functional groups to the first module) functional groups which bind to catalytic residues of a protein kinase, and attach a second module to the identified first module by substituting the second module for the peptide scaffold to form a combination of first and second module.

The specification discloses that the compounds are produced according to claim 1, and does not recite how the compounds are produced. The specification examples are drawn to specific naphthalene scaffold compounds, and indole scaffold compounds as tyrosine kinase inhibitors. The specification disclosure is drawn to specific non-peptide scaffold compounds as protein kinase inhibitors which are distinct from the claimed compounds in which the non-peptide scaffold of the second module is substituted for a peptide scaffold, resulting in a non-peptide scaffold compounds as protein kinase inhibitors. The specification description does not sufficiently teach the first module contains a peptide scaffold and the functional groups are present on the peptide scaffold or the first module is distinct from the peptide scaffold. The specification discloses compounds with non-peptide scaffold as protein kinase inhibitors, and not

the claimed method steps. The specification description clearly do not provide adequate representation regarding the open ended method of instant claim.

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that "written description of an invention involving a chemical genus, like a description a chemical species, 'requires precise definition, such as structure or formula or chemical name' of an the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997), quoting Fiers v. Revel, 25 USPQ2d 1601, 1601 (Fed. Cir. 1993)* [the claims at issue in University of California v. Eli Lilly defined the invention by function of the claimed DNA].

This holding is applicable to the present claimed method because the invention lacks showing of sufficient identifying characteristics or lacks examples of claimed method or identifying a first module whose functional groups bind to the catalytic residues of a protein kinase and attach the selected or identified first module with the functional groups to a second module of the claimed method, to demonstrate possession of claimed generic. The specification does not recite that identifying the first module comprises attaching the first module to a peptide scaffold.

The claimed method recites '.....identifying a first module having one or more functional groups each capable of covalently or non-covalently binding to catalytic residues of the protein kinase ...', however, the specification disclosure does not give sufficient guidance on how to identify the first module which have functional groups which can bind to a catalytic sites of a protein kinase. Further the instant claim recites that the '...identifying comprises covalently attaching the first module to a peptide scaffold....'. The specification does not sufficiently teach

the structure of the first module such that the starting reagents in the claimed method are known. The specification does not give any guidance on selecting the first module or how to identify the first module having functional groups capable of binding to a protein kinase or which compounds are used as first module. The recitation of 'identification comprises covalently attaching the first module to a peptide scaffold..' is confusing, and the specification does not recite those features. Neither the peptide scaffold structure nor the first module structure is known such that the first module attached to the peptide scaffold is reacted with a second module to obtain non-peptide scaffold protein kinase inhibitors.

The specification disclosure is hypothetical and based on identifying individuals scaffolds which could inhibit protein kinases and is not drawn to identifying potential first modules and attaching the identified first module to a second module such that the second module substitutes for the peptide scaffold and then screen for the combination of first and second modules as protein kinase inhibitors. The specification description is based on computer modeling studies of protein kinases and use of analogs or different functional group attachment to a first scaffold and screening for protein kinase inhibitors. However, the specification has not disclosed the claimed method of identifying the protein kinase inhibitors. The specification does not have examples of the protein kinase inhibitors identified using the claimed method. Thus the specification lacks written description of the claimed invention.

3. Claims 1, 3-8, 13-20, 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims briefly recite a method for identifying inhibitors of protein kinases comprising: identifying at least one first module having one or more functional groups each capable of covalently or non-covalently binding to catalytic residues of the protein kinase; covalently attaching the atleast one first module to at least one second module comprises an indole to form one or more combinations of the first and second modules by substituting the second module for the peptide scaffold; screening the one or more combinations of the first and second module for protein kinase inhibition; and selecting combinations o the first and second modules which inhibit protein kinase activity.

In the claimed method step of '...identifying at least one first module' or the combination of first-second modules contains no chemical structure (either the reactants or the final product) and recite vague steps (such as ".... identifying at least one first module.. comprises attaching at least one first module to a peptide scaffold; or ..... covalently attaching comprising substituting at least one second module...") without any modification of the resulting product (first module is attached to the second module by substituting the second module) from the reagents used.

The claims omit the essential structures, such as first module, protein scaffold , non-peptide scaffold and omitting structural relationship of the reagents, such omission amounting a gap between the necessary structural connections (see MPEP 2172.01). Reaction steps or compound structure which are critical or essential to the practice of the invention, but not included in the claim is not enabled by the disclosure. *See In re Mayhew, 527 F. 3d 1229, 188 USPQ 356 (CCPA 1976): Ex Parte Bhide (BdPat App&int) 42 USPQ2d.*

The factors to be considered in determination of undue experimentation are disclosed In re Wands (USPQ 2d 1400: CAFC 1988); the quantity of experimentation necessary: the amount

of direction or guidance presented; the presence or absence of working examples; the nature of the inventions; the state of the prior art; the predictability of the art and the breadth of the claims.

A number of factors would prevent one of ordinary skill in the art from practicing (making and using) the invention without undue experimentation, which are summarized as follows:

a) The specification fail to give adequate direction and/or guidance as to the means of identifying at least one first module by attaching the first module to a peptide scaffold and identifying the functional groups on the first module bind to catalytic residues of the protein kinase; and covalently attaching the selected or identified first module to a second module by substituting the non-peptide scaffold of the second module for the peptide scaffold. The specification fail to give guidance on how to identify a first module or the structure of the first module and use the identified first module covalently attached to a peptide scaffold, to attach to a second module by substituting the second module for a peptide scaffold. The specification does not give sufficient guidance on the chemical structure of the first module or the peptide scaffold or the first module attached to the peptide scaffold or the second module.

b) The specification working examples are drawn to specific compounds with either naphthalene or indole scaffold compounds as protein kinase inhibitors. The specification does not recite any compounds in which the non-peptide scaffold of the second module a substituted for a peptide scaffold and use of these compounds as protein kinase inhibitors.

c) The breadth of the claims is open ended regarding the resulting protein kinase inhibitor structure. The compounds in the specification are all drawn to non-peptide scaffold compounds, and no compounds in which the non-peptide scaffold was substituted for a peptide scaffold.

d) The state of prior art at the time the invention was made is such that the protein kinase inhibitors are specific to the kinases and in general known to be difficult resulting in non-functional compounds.

e) The art is unpredictable because organic synthesis (or modifications) and screening for active compounds is unpredictable when applied to compounds of diversity. Moreover, it is not possible to predict, a priori, the compounds that have not prepared previously, especially when the compounds are from a diverse classes of compounds which lack any core structure, that is necessary to elicit a common activity.

Accordingly, unpredictability with respect to the final compound structure, the lack of guidance presented in the specification, the lack of representative examples for making such protein kinase inhibitors necessitate the illustration or further examples demonstrating the making and use of representative sample of the compounds in order to provide the enablement for the present broadly claimed method.

4. Claims 1, 3-8, 13-20 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The newly added limitation '...wherein said identifying one or more functional groups on the first module which preferentially bind to catalytic residues of the protein kinase;.....'; and 'wherein said covalently attaching comprises substituting the at least one second module for the peptide scaffold.' Claimed in claim 1 has no clear support in the specification and the claims as

originally filed. The subject matter claimed in claim 1 broadens the scope of the invention as originally disclosed in the specification.

If applicants disagree, applicants should present a detailed analysis as why the claimed subject matter has a clear support in the specification. Applicants response filed 7/31/03 has not provided the support for the amendments in the specification.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 3-8, 13-20, 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites identifying a t least one first module, however it is not clear what is a first module. Does applicants mean that the first module is a functional group or peptide scaffold? The specification does not have a specific definition for a first module. Is the module is same as scaffold. Applicants are requested to clarify.

Claim 1 recites that the 'identifying a first module comprising ... first module having one or more functional groups each capable of covalently or non-covalently binding to a catalytic residues of the protein kinase..'and 'identifying comprises covalently attaching the at least one of first module to a peptide scaffold and identifying one or more functional groups on the first module which preferentially bind to catalytic residues of the protein kinase...'. It is not clear whether the protein kinase to which the functional groups of the first module preferentially bind is same as the peptide scaffold to which the first module is covalently attached. It is not clear

what is relationship between the functional groups on the first module, peptide scaffold and the protein kinase. It is also not clear from the claimed method the 'identifying the first module' comprises that the attaching the first module to a peptide scaffold and the functional groups on the first module bind to the protein kinase. That is in the 'identifying the first module' step comprises forming a complex structure with a peptide scaffold- first module- protein .

Further claim 1 recitation is indefinite by reciting '... covalently attaching at least one first module to at least one second module which provides a non-peptide scaffold ..... .comprising substituting the at least one second module for a peptide scaffold...', it is not clear what is the resulting end product of covalently attaching the first module to a second module by substituting the second module non-peptide scaffold for a peptide scaffold. It is not clear what is the structure of the second module, does applicant mean the second module has a non-peptide scaffold, or provides means gives off non-peptide scaffold or indole and a non-peptide scaffold or indole is the non-peptide scaffold or indole + non-peptide scaffold. Applicants are requested to clarify. The claimed method steps are very confusing and the resulting protein kinase inhibitor structure is not predictable or determinable from the claim limitations.

Claim 1 is vague and indefinite by reciting 'preferentially', 'covalently attaching comprises substituting', 'provides'... which are not clear what does applicants mean by. Applicants are requested to use an alternative language.

Claim 1 recites the limitation "the protein kinase" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a

gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the claim does not recite how the first module and second module are attached, and/or the chemical structure of the first module and/or the functional groups of the first module and protein kinase and the peptide scaffold. The claim does not recite how all these reagents are linked together such that the resulting compounds inhibit protein kinases .

Response to Arguments

7. Applicant's arguments with respect to claims 1, 3-8, 13-20, 22 filed on 7/31/03 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

8. No claims are allowed.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. WO 95/04277 (Pavia et al) teaches method for preparing and selecting pharmaceutically useful non-peptide compounds (no indole scaffold compounds as in the instant claims) from a structurally diverse universal library. The reference teaches the exact method steps, however do not teach two different modules in preparation of protein kinase inhibitors.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padmashri Ponnaluri whose telephone number is 703-305-3884. The examiner is on Flex Schedule and can normally be reached on Monday through Friday from 7 AM and 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 703-306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

Padmashri Ponnaluri
Primary Examiner
Art Unit 1639

Pp
09 October 2003

PADMASHRI PONNALURI
PRIMARY EXAMINER